Table WEB-1: DINP, General Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Animal Number/ Sex	Dose*	Body Weight	Organ Weight**	Liver Effects	Hematology	Other
Fischer 344 Rat BIBRA 1985 (*1*)	Subchronic study – 21 days. Rats (~41–43 days old) were fed diets with 0, 0.6, 1.2, or 2.5% DINP and then sacrificed and necropsied. Peroxisome proliferation was studied by electron microscopy examination of liver and measurement of peroxisomal enzyme activity.	5	0					
		5	639(M)/ 607(F)	NE	↑Li, Ki	↑11-OH(M) and 12-OH(M). ↑Protein.	NA	↓Serum Ch, Tg(M).
		5	1,192(M)/ 1,193(F)	↓	↑Li, Ki	↑PCoA(M), 11-OH and 12-OH(M). ↑Protein. Histological changes.	NA	↓Serum Ch, Tg(M). ↑Serum Tg(F).
		5	2,195(M)/ 2,289(F)	↓	↑Li, Ki, Te	↑PCoA, 11-OH and 12-OH. ↑Peroxisomes. ↑Protein. Histological changes.	NA	↓Serum Ch, Tg(M). ↑Serum Tg(F). No dose-related testicular lesions.
	↑A group of positive control rats was administered DEHP at 1.2%.	5	*1,084(M)/ 1,063(F)*	–	*-Li, Ki*	*↑PCoA, 11-OH and 12-OH.* *↑Peroxisomes.* *↑Protein.*	*NA*	*↓Serum Ch, Tg(M).* *No dose-related testicular lesions.*

*Dose measured in mg/kg bw/day.
**Organ to body weight ratio.

NA=Not Analyzed
NE=No Effects
F=Female
M=Male
↑= Statistically Significant Increase
↓=Statistically Significant Decrease
Te=Testes
PCoA=Palmitoyl-CoA Oxidase
Tg=Triglyceride
Ch=Cholesterol
Li=Liver
Ki=Kidney
11-OH=11-Hydroxylase
12-OH=12-Hydroxylase
PCoA=Palmitoyl-CoA Oxidase Activity

Table WEB-2: DINP, General Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Animal Number/ Sex	Dose*	Body Weight	Organ Weight**	Liver Effects	Hematology	Other
Fischer 344 Rat Lington et al. 1997 (*2*)	Chronic study – 2 years. 6-week-old rats were fed diets with 0, 0.03, 0.3, and 0.6% DINP-1 for 2 years. 10 rats/sex/group were sacrificed and necropsied at 6, 12, and 18 months and the rest were killed and necropsied at the end of the study. Hematology, serum chemistry, and urinalysis were evaluated every 6 months. Peroxisome proliferation was examined microscopically in 2 rats/sex/group at 24 months.	110 110 110 110	0 15(M)–18(F) 152(M)–184(F) 307(M)–375(F)	NE ↓(M; 18–24 mo). ↓(M; 12–24 mo).	NE ↑Li, Ki (6–24 mo). ↑Li, Ki (6–24 mo). ↑Sp (24 mo). ↑Ad (24 mo)	NE Hepatic lesions (24 mo). ↑SGOT (M; 6–12 mo), SGPT (M; 24 mo). ↑MNCL. Hepatocyte enlargement (6–24 mo) and lesions (24 mo). ↑SGOT (M; 6–18 mo), SGPT(M; 6 and 18 mo). ↑MNCL. No evidence of peroxisomal proliferation	NE NE ↓RBC, Hb, Hct (M; 24 mo)	NOAEL ↓Survival (F). ↓Survival (F). ↑ Urine volume (M; 6–24 mo). ↑ Urine K and glucose (M; 6–18 mo). No evidence of testicular damage.

*Dose measured in mg/kg bw/day.

NA=Not Analyzed
NE=No Effect
↑= Statistically Significant Increase
↓=Statistically Significant Decrease
Sp=Spleen
M=Male
F=Female
Li=Liver
Ki=Kidney
K=Potassium
RBC=Red Blood Cell
Hb=Hemoglobin
Hct=Hematocrit
Ad=Adrenal
SGOT=Serum Glutamic Oxaloacetic Transaminase
SGPT=Serum Glutamic Pyruvic Transaminase
MNCL=Mononuclear Cell Leukemia
Mo=Months

Table WEB-3: DINP, General Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Animal Number/ Sex	Dose	Body Weight	Organ Weight**	Liver Effects	Hematology	Other
F344 Rats Moore 1998 (*3*)	Chronic study – 2 years. 6-week old rats were fed diets with 0, 500, 1,500, 6,000, or 12,000 DINP. 5 rats/sex/dose were killed on weeks 1, 2, and 13; 15 rats/sex/dose were killed at 79 weeks; and 55 rats/sex/group at 104–106 weeks. Clinical evaluations (hematology, serum chemistry, and urinalysis) were conducted every 26 weeks. Peroxisome proliferation was examined in 5 rats/sex only in the controls and high dose group during weeks 1, 2, and 13 and in 3–5 rat/sex in the control, 359–442 mg/kg bw/day group, and high-dose group at week 104.	85 70	0 29.2(M)/ 36.4(F)	NE	NE	NE	NE	NE
		70	88.3(M)/ 109(F)	NE	NE	NE	NE	NOAEL
		85	359(M)/ 442(F)	NE	↑Ki (wk 79–104). ↑Li (wk 1–104).	↑PCoA (F, wk 104). ↑ASAT, ALAT (wk 52, 78, 104).	↑Anemia.	Kidney lesions (M, wk 79–104). ↑ Serum urea (wk 26–104). MNCL (wk 104).
		85	733(M)/ 885(F)	↓ (wk 9–104)	↑Ki (wk 79–104), Li (wk 1–104).	↑PCoA (wk 1–104). Lesions (wk 2–104). Neoplasia (M, wk 79–104). ↑ASAT, ALAT (wk 52, 78, 104). ↓ASAT, ALAT (F, wk 26).	↑Anemia.	↓Survival (M). ↑Serum urea (wk 26–104). ↑Urine vol with ↓Cl, Ca, K and Cre(M, wk 104). Kidney lesions (wk 79–104). Kidney neoplasm (M, wk 104). MNCL (wk 104). No testicular effects.
	A group of 55 rats/sex was exposed to the high dose for 78 weeks and sacrificed at 105–106 weeks to study recovery effects.*	55	637(M)/ 774(F)	↓(F)	↑Ki(F)		NE	↑Urine vol with ↓ Cre(M). MNCL (wk 104). Kidney lesions and neoplasm (M).

*Only effects observed by week 104 were listed.
**Organ to body weight ratio.

M=Male
NE=No Effects
↑= Statistically Significant Increase
↓=Statistically Significant Decrease
K=Potassium
F=Female
Li=Liver
Ki=Kidney
Ca=Calcium
Cre=Creatinine
PCoA=Palmitoyl-CoA Oxidase
Cl=Chloride
MNCL=Mononuclear Cell Leukemia
wk=Week
ASAT=Aspartate aminotransferase
ALAT=Alanine aminotransferase
vol=Volume

Table WEB-4: DINP, General Toxicity, Mice

Species, Strain, and Source	Experimental Regimen	Animal Number/ Sex	Dose[a]	Body Weight	Organ Weight**	Liver Effects	Hematology	Other
$B6C3F_1$/ CrlBR mice Moore 1998 (*4*)	Chronic study – 2 years. 6-week-old mice were fed diets with 0, 500, 1,500, 4,000, and 8,000 ppm DINP. 15 mice/dose/ sex were evaluated and sacrificed at 79 weeks and 55 mice sex/group at 105–106 weeks. Clinical evaluations (hematology, serum chemistry, and urinalysis) were conducted every 26 weeks. Peroxisome proliferation was examined in 5 mice/sex in the highest dose group and controls during the midpoint and end of study.	70	0					
		70	90.3(M)/ 112(F)	NE	NE	NE	NE	NOAEL (F)
		70	276(M)/ 336(F)	NE	NE	↑Neoplasia (F).	NE	NOAEL (M)
		70	742(M)/ 910(F)	↓ (wk 1–104)	↓Ki(M), ↑Li(M) (wk 79–104).	↑Neoplasia (M).	NE	NE
		70	1,560(M)/ 1,888(F)	↓ (wk 1–104)	↓Ki (M), ↑Li (wk 79–104).	↑Neoplasia and non-neoplastic changes. ↑Serum AST, ALT (M). ↑PCoA (week 79–104).	↓WBC (wk 26–98).	↓Survival (M). ↑Nephropathy(F). ↑Serum protein (M, week 104). ↑Urinary vol with ↓Na, Cl, K (week 52–104). No effects on testicular histology.
	A group of 55 mice/sex was exposed to the high dose for 78 weeks and sacrificed at 105–106 weeks to study recovery effects.*	55	1,377(M)/ 1,581(F)	↓(M)	↓Ki(M).	↑Neoplasia.	NE	NE

[a] Dose measured in mg/kg bw/day.
*Only effects observed by week 104 were listed.
**Organ to body weight ratio.

M=Male
NE=No Effects
↑= Statistically significant increase
↓=Statistically significant decrease
WBC=White Blood Cell
F=Female
Li=Liver
Ki=Kidney
Ep=Epididymis
Te=Testes
PCoA=Palmitoyl-CoA Oxidase
Trans=Transient
Cre=Creatinine
Na=Sodium
Cl=Chloride
K=Potassium
ASAT=Aspartate Amino Transferase
ALAT=Alanine Amino Transferase
vol=volume

Table WEB-5: DINP, General Toxicity, Marmosets

Species, Strain, and Source	Experimental Regimen	Animal Number/Sex	Dose*	Body Weight	Organ Weight	Histopathology	Hematology	Chemistry	Other
Marmoset Hall et al. 1999 (5)	Subchronic study – 13 Weeks. Male and female marmosets (16–25 months old) were gavaged with DINP in 1% methylcellulose and 0.5% Tween. Clofibrate was used as a positive control. Parameters evaluated at sacrifice included estradiol and testosterone concentrations, biochemical evidence of peroxisomal proliferation, and organ weights and histopathology.	1–2 2 2 2 *1–2*	0 100 500 2,500 *500 Clofibrate*	 NE NE decrease[a] *decrease[a]*	 NE NE NE *- Ki to body weight ratio[a]*	 NE NE NE *NE*	 NE NE NE *- Anemia*	 NE NE No change in PCoA *- PCoA* *- 11-OH*	 Ungroomed coat and reddening of the skin. Thin appearance, hunched posture and reduced activity in one male.[a]

*Dose measured in mg/kg bw/day.
[a]Effects were not statistically significant.

NE=No Effects
M=Male
F=Female
↑11-OH = Lauric acid 11-hydroxylase activity
↑=Statistically Significant Increase
PCoA=Palmitoyl-CoA Oxidase activity

Table WEB-6: DINP Developmental Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[b]	Dose[d]	Maternal Effects	Fetal Effects
Wistar Rat Hellwig et al. 1997 (*7*)	Prenatal developmental toxicity study. Three types of DINP[a] manufactured by different processes were administered in oil by gavage on gd 6–15. Dams were weighed on gd 0, 6, 10, 15, and 20 and sacrificed on gd 20. Maternal uteri were weighed, corpora lutea were counted and implantation sites examined. Fetuses were weighed and examined for gross external malformations. Half of the fetuses were examined for visceral malformations and the other half for skeletal malformations.	9 9–10 8–10 9–10	0 40 200 1,000	 ↑Kidney to bodyweight ratio in DINP-2. ↓Implantation sites/litter in DINP-2. NE ↑Kidney to bodyweight ratio in DINP-1. ↑Liver to bodyweight ratio in DINP-3.	 ↓Live fetuses/litter in DINP-2. NE ↑Fetuses/litter with cervical ribs in: DINP-1: 11 fetuses in 5 litters vs 0 fetuses DINP-2: 4 fetuses in 4 litters vs 0 fetuses DINP-3: 12 fetuses in 7 litters vs 0 fetuses. ↑Fetuses/litter with lumbar ribs in: DINP-1: 37 fetuses in 10 litters vs 0 fetuses DINP-2: 10 fetuses in 5 litters vs 0 fetuses DINP-3: 34 fetuses in 8 litters vs 0 fetuses. ↑Fetuses/litter with hydroureter in DINP 3: 12 fetuses in 8 litters vs 4 fetuses in 3 litters. ↑Fetuses/litter with malformations in DINP-3 (7.3 vs 4.3%).[c] ↑ Dilated renal pelves in DINP-1,2,3.

[a](1) CAS RN: 68515-48-0; (2) CAS RN: 28553-12-0; (3) CAS RN: 28553-12-0 (2 and 3 by different manufacturing process).
[b]Number of litters examined per type of DINP.
[c]Skeletal and visceral malformations (humorous, femur, kidney, and ureter); not statistically significant.
[d] Dose measured in mg/kg bw/day.

↑=Statistically Significant Increase ↓=Statistically Significant Decrease NE=No Effect

Table WEB-7: DINP, Developmental Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number*	Dose**	Maternal Effects	Fetal Effects
Sprague-Dawley Rat Waterman et al. 1999 (*8*)	Prenatal developmental toxicity study. DINP-1 administered in oil by gavage on gd 6–15. Sacrificed on gd 21. Dams weighed on gd 0, 6, 9, 12, 15, 18, and 21. Maternal uterus and ovaries were weighed, corpora lutea were counted and implantation sites examined. Fetuses were weighed, sexed, and examined for gross external malformations. Half of the fetuses were examined for visceral malformations and the other half for skeletal malformations.	24 25 24 23	0 100 500 1,000	NE NOAEL ↓ Weight gain (transient). ↓ Food intake (transient).	↑ % Fetuses with dilated renal pelves (3.7 vs 0%). ↑ % Fetuses with dilated renal pelves (4 vs 0%). ↑ % Fetuses with lumbar ribs (19 vs 4%). ↑% Litters with dilated renal pelves (26 vs 0%). ↑ % Fetuses with dilated renal pelves (4.5 vs 0%). ↑ % Litters with lumbar ribs (78 vs 25%). ↑ % Fetuses with lumbar ribs (35 vs 4%). ↑ % Fetuses with cervical ribs (6 vs 2%).

*Number of litters examined.
** Dose measured in mg/kg bw/day.
↑=Statistically Significant Increase ↓=Statistically Significant Decrease NE=No Effect

Table WEB-8: DINP, Reproductive Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Animal Number/ Sex	Dose*	Effects
CD Rats Waterman et al. 2000 (*9*)	Two generation reproductive toxicity study. DINP administered in feed for 10 weeks prior to mating at 0, 0.2, 0.4, or 0.8%. Males treated until delivery of last litter and females through gestation to lactation. Breeding pairs housed together for 3 weeks; body weight and food intake was measured weekly. One male and female from each litter reared to adulthood and remaining pups were examined and discarded.	30	0	
		30	165/182/146/254	↑Kidney weight in F_0 females. ↓Weight gain in F_1 pups.
		30	331/356/287/539	↑Liver weight in F_0 females. ↑Kidney weight in F_0 males and females. ↓Weight gain in F_1 pups.
		30	665/696/555/1,026	↓Weight gain in F_0 females (pnd 14, 21). ↑Liver weight in F_0 males and females. ↑Kidney weight in F_0 males and females. ↓Left ovary weight in F_0 females. ↓Weight gain in F_1 pups. No effect on weights of male reproductive organs, testicular histology, or litter size, mating, offspring survival, and sex ratio.
	One male and female F_1 rat/litter continued to receive the same doses as parental rats and were then mated within dose groups during adulthood.	30	189/197/143/285	NE
		30	379/397/288/553	↓F_2 pup weight gain during lactation.
		30	779/802/560/1,129	↓Body weight in F_1. ↑Liver weight in F_1 females and kidney weight in F_1 males. ↓F_2 pup weight gain during lactation. No effects on mating, fertility, litter size, pup weight, survival, or sex ratio, sex organ weights or testicular histology.

*Doses (in mg/kg bw/day) in males during premating/females during premating/females during gestation/females during lactation.
↑=Statistically Significant Increase ↓=Statistically Significant Decrease

Web Table-9 : DINP, General Toxicity, Monkeys

Species, Strain, and Source	Experimental Regimen	Animal Number/Sex	Dose*	Body Weight	Organ Weight	Histopathology	Hematology	Chemistry	Other
Cynomolgus monkey Pugh et al. 2000 (*6*)	Subacute study – 2 weeks. 2-year-old males were gavaged with DINP in 0.5% methylcellulose for 2 weeks and then sacrificed and necropsied.	4 4	0 500	NE	No effects on organ to body-weight ratios	No testicular or hepatic lesions.	↑ Neutrophils ↓ Lymphocytes	NE	No peroxisome proliferation. No effects on gap junctional intracellular communication.

*Doses measured in mg/kg bw/day.
NE=No Effects
↓=Statistically Significant Decrease
↑= Statistically Significant Increase

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